*Review*

# Regulation of NLRP3 by non-coding RNAs in different cancers: interplay between non-coding RNAs and NLRP3 in carcinogenesis and metastasis

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**Abstract:** NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasomes are multitasking intracellular sensors having characteristically unique ability to detect myriad of microbial motifs and endogenous danger signals which promote structural assembly of NLRP3 inflammasome thus enabling it to perform instrumental roles. Detailed mechanistic insights revealed that molecularly assembled NLRP3 inflammasomes stimulated caspase-1-driven release of the pro-inflammatory cytokines. NLRP3 has been shown to play fundamental role in the regulation of cancer progression and metastasis. Recently emerging cutting-edge research-works have started to shed light on the involvement of non-coding RNAs in the regulation of NLRP3 in different cancers. MicroRNAs, lncRNAs and circular RNAs have been shown to modulate NLRP3 in different diseases. However, we still have incomplete information about regulation of NLRP3 by circular RNAs in various cancers. In this review, we will comprehensively analyze how different microRNAs and long non-coding RNAs modulate NLRP3 in human cancers. Emerging evidence has started to scratch the surface of the participation of miRNAs and lncRNAs in the regulation of NLRP3. Xenografted mice-based studies have also enabled us to develop a better comprehension of interplay between miRNAs, lncRNAs and NLRP3. Hopefully, detailed analysis of contextual regulation of NLRP3 by oncogenic and tumor suppressor miRNAs, lncRNAs and circRNAs will be helpful in getting a step closer to the personalized medicine.

*Key words:* NLRP3; Molecular cancer; Signaling; Non-coding RNA.

## Introduction

Pioneering research works have uncovered mysteries related to NLR family, pyrin domain-containing 3 (NLRP3) inflammasome. Series of genomic and proteomic studies have helped us in the dissection of molecular aspects of NLRP3 inflammasome. NLRP3 is a multi-protein machinery that triggers activation of caspase 1 (1,2). Resultantly, caspase 1 activation further promoted processing and secretion of the pro-inflammatory cytokines for example interleukin-1β and interleukin-18. Genomic and proteomic studies had shown that during normal situations, NLRP3 remained auto-repressed mainly through an interaction between LRRs and NACHT domain. However, this auto-repression was de-repressed by DAMPs (damage-associated molecular patterns) from endogenous danger signals or PAMPs (pathogen associated molecular patterns). Exposure to DAMPs or PAMPs induced oligomerization of NLRP3 and recruited ASC/PYCARD (apoptosis-associated speck-like protein containing a CARD) and pro-caspase 1, which triggered caspase-1 activation and consequential maturation and secretion of interleukin-1β and interleukin-18 (1,2).

NLRP3 has been shown to play key role in carcinogenesis. We will summarize some of the most important discoveries associated with mechanistic insights of NLRP3 which have leveraged our understanding altogether to a new level.

Sphingolipid sphingosine-1-phosphate (S1P) promoted survival, migration and proliferation of cancer cells (3). Deficiency of S1PR1 in macrophages prevented pulmonary metastasis and tumor lymphangiogenesis. NLRP3 expression was noted to be reduced in S1PR1-deficient tumor-associated macrophages. Lymph node invasion and distant metastases were interconnected significantly with a higher NLRP3+ macrophage infiltrate (3).

Human breast cancer-associated fibroblasts (CAFs) have higher NLRP3 expression (4). NLRP3 depletion in CAFs severely impaired the recruitment of the monocytic fractions of CD11b+Gr1+ cells into mammary tumors. Injection of NLRP3-depleted or IL-1β-depleted fibroblasts significantly attenuated tumor growth and weight in xenografted mice. Lung metastatic lesions were found to be notably reduced in mice injected with IL-1β-depleted fibroblasts (4).

It was astonishing to note that exposure of macrophages to conditioned media from colorectal cancer cells induced NLRP3 expression in macrophages (5).

Use of glibenclamide (NLRP3 antagonist) and a caspase-1 antagonist inhibited NLRP3 inflammasome-mediated chemotactic movement of SW480 cells. MC38 colon cancer cells were injected into the spleen of mice to generate a models of liver metastasis. Findings suggested that NLRP3$^{-/-}$ mice demonstrated fewer liver metastasis nodes, less hepatic dissemination and metastatic spread of cancer cells (5).

5-FU-mediated increase in the levels of intracellular ROS stimulated the expression and activation of NLRP3 (6). Levels of NLRP3 and IL-1β were noted to be enhanced in 5-FU-treated CAL27 and WSU-HN6 cells. 5-FU induced regression of tumors in mice xenografted with NLRP3-silenced CAL27 and WSU-HN6 cells. 5-FU was found to be effective against chemically induced tongue squamous carcinoma models. These models were NLRP3$^{-/-}$ and caspase1 $^{-/-}$ and 5-FU was given to analyze its cancer preventive effects in the absence of NLRP3. 5-FU delayed the occurrence of tongue carcinoma and tumor areas were notably smaller (6).

Structural interactions of TRIM59 with ABHD5 (ab-hydrolase domain containing-5) promoted the ubiquitination of ABHD5 and consequent proteasome dependent degradation of ABHD5 (7). Lung cancer cells-derived exosomes are rich in TRIM59. Moreover, TRIM59 can be exosomally transported to macrophages. ABHD5 deficiency caused the activation of NLRP3 inflammasome in macrophages. There was marked increase in the activation of NLRP3 in ABHD5-silenced THP-1 macrophages (7).

Tumor cell-derived IL-1β promoted the activation and secretory phenotype of quiescent pancreatic stellate cells. Tumor cell-derived IL-1β was also essential for the maintenance of an immunosuppressive milieu (8). Whereas, loss of tumor cell-derived IL-1 cascade in tumor stroma enabled intra-tumoral infiltration and activation of CD8+ cytotoxic T cells, attenuation of the growth of pancreatic cancer and conferred survival advantage to PDA-bearing mice. Knockdown of NLRP3 in KRas$^{G12D}$-pancreatic ductal epithelial cells and KPC cells produced interesting results. NLRP3 depletion in the transformed ductal epithelia significantly reduced IL-1β production and cleaved caspase-1 expression in IL-1β-sh KRas$^{G12D}$-PDEC pancreatic grafts. There was a marked reduction in the growth of IL-1β-sh KRas$^{G12D}$-PDEC pancreatic grafts as well as increased overall survival and decreased tumor growth of orthotopic IL-1β-sh KPC tumor-bearing mice (8).

Myeloid-derived suppressor cells (MDSCs) (CD11b$^+$ Gr-1$^+$) have high expression of NLRP3 and pro-IL-1β (9). IL-1β secretion triggered by 5-FU in MDSC was dependent on the activation of NLRP3 inflammasome. MSC-2 cells have basal expression of the components of NLRP3 inflammasome. Docosahexaenoic acid promoted the interaction between NLRP3 and β-arrestin-2 in 5-FU-treated MDSC. MDSC obtained from 5-FU-treated tumor-bearing mice and fed on a docosahexaenoic acid-enriched diet demonstrated low activity of caspase 1 (9).

Considerably higher levels of NLRP3, ASC, caspase-1 and IL-18 were reported in Tgfbr1/Pten double conditional knockout (2cKO) SCCHN mice tumor lysates (10). Findings clearly suggested that NLRP3 was functionally active in Tgfbr1/Pten 2cKO SCCHN animal models. Chemical inhibition of NLRP3 by MCC950 caused a delay in the tumor formation in Tgfbr1/Pten 2cKO SCCHN models (10).

MDSCs obtained from tumor bearing caspase 1–deficient (Casp 1$^{-/-}$) mice treated with 5-fluorouracil did not produce IL-1β (11). These findings supported the notion that 5-fluorouracil and gemcitabine triggered activation of caspase-1 in MDSCs that resulted in the secretion of IL-1β. 5-fluorouracil and gemcitabine induced activation of caspase-1 in MDSCs from wild-type but not in Nlrp3 deficient animal models. MDSCs obtained from Nlrp3$^{-/-}$ tumor bearing mice also did not produce IL-1β after treatment with 5-fluorouracil or gemcitabine. Collectively, these findings suggested that 5-fluorouracil and gemcitabine-mediated antitumor effects were more pronounced in Casp1$^{(-/-)}$ or Nlrp3$^{(-/-)}$ mice or wild-type mice treated with interleukin-1 receptor antagonists (11).

Certain hints have emerged which highlight the activation of NLRP3 inflammasome in platelets (12). Activation of NLRP3 caused the aggregation of the platelets. Intraperitoneal injections of the MCC950 (NLRP3 inhibitor) caused significant suppression of platelet caspase-1 activity in tumor bearing animal models. Furthermore, platelet activation and aggregation were suppressed significantly in tumor-bearing mice transfused with NLRP3$^{-/-}$ platelets. Orthotopic injections of Panc02 cells into NLRP3$^{-/-}$ mice resulted in decreased tumor weights (12).

**Tumor suppressor role of NLRP3**

Tumor suppressive activities of NLRP3 have also been reported. Different scientific reports have provided clues about tumor suppressive effects of NLRP3.

PTEN interacted and dephosphorylated NLRP3 through its protein-phosphatase activity and facilitated activation of NLRP3 (13). MTX induced caspase-1 cleavage in the tumor tissues of wild-type mice but not in Pten-knockout mice. MTX induced production of IL-1β and IL-18 was also noted to be suppressed in the tumor tissues from Pten-knockout mice or NLRP3 knockout mice. NLRP3$^{Y32D}$ or NLRP3$^{Y32E}$ lost the ability to interact with ASC which supported the notion that NLRP3 dephosphorylation at tyrosine 32 was a necessary for NLRP3–ASC interactions. NLRP3$^{Y30E/Y30E}$ mice were resistant to MTX-mediated regression of the tumors (13).

Transplantable tumor cells derived from a murine primary colon carcinoma (MC38) were intrasplenically injected in a C57BL/6 syngenic immunocompetent host that lead to liver metastasis (14). MC38-derived conditioned media robustly primed the inflammasome responses. There was an evident increase in caspase-1 activity and secretion of IL-18 and IL-1β. NLRP3$^{-/-}$ mice phenocopied Ice$^{-/-}$ mice and demonstrated higher tumor burden in the liver (14).

LXRα knockdown upregulated the expression of NLRP3 in clear cell renal carcinoma (ccRCC) cells, while overexpression of LXRα caused downregulation of NLRP3 (15). Migratory and invasive potentials of NLRP3-silenced ccRCC cells were noted to be markedly enhanced. Metastatic neoplasm numbers were

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found to be reduced in the livers of mice inoculated with LXRα-knockdown 786-O cells. Another dimension of liver metastasis was analyzed in mice intrasplenically injected with LXRα- knockdown cancer cells. Degree of liver metastases was remarkably reduced in mice injected with LXRα- knockdown cancer cells (15).

In this review we have attempted to highlight open questions and knowledge gaps of research that warrant further exploration to gain a comprehensive cellular and molecular knowledge of the regulatory role and interplay between non-coding RNAs and NLRP3 in human cancers.

## Regulation of NLRP3 by non-coding RNAs

Breakthroughs in our rapidly evolving knowledge related to the regulation of NLRP3 by non-coding RNAs has added another layer of complexity to already complicated role of NLRP3 in different cancers. Non-coding RNAs have been shown to portray multi-layered regulation of NLRP3 in different cancers. In this section, we will exclusively focus on different miRNAs and lncRNAs reportedly involved in the regulation of NLRP3 in human cancers. Substantial fraction of information has already been added into the web of molecular oncology related to "sponge effects" of lncRNAs which inhibit and promote carcinogenesis and metastasis. LncRNAs play contributory role either by promoting or repressing the expression of NLRP3. Therefore, we have partitioned following section into sub-headings. In the first section, we will exclusively analyze how different miRNAs modulate NLRP3 expression in diverse cancers. Later, we will provide an overview of the regulation of NLRP3 by lncRNAs.

## Regulation of NLRP3 by microRNAs

### miR-22

miR-22 has been shown to exert tumor suppressive effects mainly through negative regulation of NLRP3 in various cancers.

miR-22 overexpression caused downregulation of NLRP3 in WSU-HN6 cells, while miR-22 inhibitors induced upregulation of NLRP3 in SCC25 cells (16). miR-22 overexpression significantly reduced the proliferation potential of WSU-HN6 cells. There was a notable shrinkage of the tumors in mice inoculated with miR-22-overexpressing oral squamous cell carcinoma cells (16).

NLRP3 binding sites are present within promoter region of CCND1 (17). NLRP3 transcriptionally upregulated CCND1 and promoted proliferation capacity of gastric cancer cells. MiR-22 agomirs were transfected into NLRP3-overexpressing BGC-823 cells and injected into the mice. Later, miR-22 was injected intratumorally and induced shrinkage of the tumors. Expression levels of NLRP3 and CCND1 were noted to significantly reduced in the tumors of xenografted mice (17).

Expression levels of NLRP3, IL-1β, MMP2, MMP9, vimentin, and N-cadherin were lower in miR-22-overexpressing and NLRP3-silenced cancer cells (18). Tumor growth was noted to be significantly reduced in mice injected with miR-22-overexpressing HCT116 cells (18).

There was an increase in E-cadherin and simultaneous reduction in the level of N-cadherin in miRNA-22 mimic-transfected SKOV3 cells (19). In addition, levels of p-PI3K and p-AKT were also noted to be reduced in miRNA-22 mimic-transfected SKOV3 cells (19).

### miR-223

Bases 406-412 of the 3′-UTR of NLRP3 mRNA have been reported to serve as a binding site for miR-223. Levels of NLRP3, caspase-1, IL-1β and IL-18 were noted to be reduced in miR-223-overexpressing hep3B cells (20). Likewise, miR-223-3p overexpression markedly reduced proliferative and migratory capacity of U251 and U87 cells (21).

There was evident shrinkage of tumors in mice injected with miR-223-transfected MCF7 cancer cells (22).

## Regulation of NLRP3 by lncRNAs

### Tumor suppressor role of NLRP3

ADAMTS9-AS2 overexpression markedly increased cisplatin mediated cytotoxic effects in drug resistant-gastric cancer cells, but these effects were reversed upon overexpression of miR-223-3p (23). RNA pull-down assay clearly provided the evidence of the direct association between 3'UTR of NLRP3 mRNA and miR-223-3p. Furthermore, ADAMTS9-AS2 effectively blocked miR-223-3p-mediated targeting of NLRP3. ADAMTS9-AS2 upregulation induced pyroptotic cell death in cisplatin treated drug resistant-gastric cancer cells by upregulation of NLRP3 inflammasome. ADAMTS9-AS2 overexpression also inhibited vimentin and N-cadherin, while promoted the expression of E-cadherin in gastric cancer cells (23).

It has recently been convincingly revealed that an oncogenic lncRNA XIST interfered with TGF/SMAD signaling in non-small cell lung cancer cells (24). XIST interacted with SMAD2 and blocked its nuclear accumulation. SMAD2 has been shown to transcriptionally upregulate NLRP3. There was an evident increase in the levels of NLRP3, caspase-1, IL-1β, and IL-18 in cisplatin-treated A549 cells. XIST has been shown to inhibit apoptosis and pyroptosis. SMAD2 transcriptionally upregulated NLRP3 and p53 but these interactions were abrogated by XIST. Cisplatin induced shrinkage of the tumors in mice inoculated with XIST-silenced A549 cells. Overall, these findings clearly indicated that XIST blocked nuclear accumulation of SMAD2 and inhibited the expression and activation of NLRP3 (24). Therefore, therapeutic targeting of XIST will be advantageous in the activation of SMAD2-driven signaling and consequent upregulation of NLRP3.

LncRNA-XIST knockdown promoted reactive oxygen species (ROS) production and consequent activation of NLRP3 inflammasome (25). In addition, there was an evident increase in the cleaved caspase-1 as well as mature IL-1β in LncRNA-XIST knockdown-A549 cells. Superoxide dismutase 2 (SOD2) has been shown to lower oxidative stress. Whereas, SOD2 inactivation markedly enhanced oxidative stress. LncRNA-XIST interfered with miR-335-mediated targeting of SOD2. However, knockdown of LncRNA-XIST promoted miR-335-mediated inhibition of SOD2 and enhanced oxidative stress in A549 cells. Collectively

these findings suggested that LncRNA-XIST promoted the expression of SOD2 and exerted inhibitory effects on NLRP3 (25). Oxidative stress induced activation of NLRP3 was necessary to inhibit cancer.

### Oncogenic role of NLRP3

NLRP3 was located at about 25 kb downstream to the XLOC_000647 (26). Findings clearly suggested that XLOC_000647 negatively regulated NLRP3 expression. Overexpression of XLOC_000647 decreased cell proliferation and invasion. NLRP3 overexpression restored invasive capacity of the pancreatic cancer cells. Tumor growth was noted to be remarkably reduced in mice injected with MIA-PaCa-2 and BxPC-3 cells stably expressing XLOC_000647. XLOC_000647 overexpression considerably reduced expression of NLRP3 in tumor tissues of the xenografted mice (26).

RGMB-AS1 interfered with miR-22-mediated targeting of NLRP3 and promoted cancer progression (27). Tumor growth was considerably reduced in mice xenografted with RGMB-AS1-silenced Hep2 cancer cells. Expression levels of RGMB-AS1 and NLRP3 were noted to be decreased whereas miR-22 expression was found to be enhanced in tumor tissues of xenografted mice (27).

Notable shrinkage of the tumors was observed in mice injected with DANCR-silenced MIA PaCa-2 cancer cells (28). miR-135a-5p levels were found to be upregulated in the tumor tissues. Whereas, NLRP3 was noted to be downregulated in the tumors of xenografted mice (28).

### Concluding remarks

Breakthroughs in the development of specified NLRP3 inhibitors are capturing the attention of basic and clinical researchers. Accordingly, development of MCC950 and caspase-1 inhibitors have opened exciting and new horizons for translational medicine (29, 30). These insights have provided basis for the rational development of novel and superior NLRP3-inhibiting compounds to target this inflammasome in human cancers. The seminal research-works summarized in this review will be useful in the development of a roadmap for the design of specific anticancer therapies by modulation of inflammasome signaling. There has been a paradigm shift in our understanding related to NLRP3 and its central role in regulation of carcinogenesis and metastasis. NLRP3 inflammasome-mediated signaling has been extensively investigated but most research efforts in this field have been focused on central role of NLRP3 in carcinogenesis and regulation of NLRP3 by miRNAs and lncRNAs, leaving big knowledge gaps about role of circular RNAs in regulation of NLRP3 in different cancers.

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